

# National Institutes of Health

## Clinical Research Policy Analysis and Coordination Program

*Fostering Simplicity, Clarity, and  
Efficiency in Clinical Research Policy*

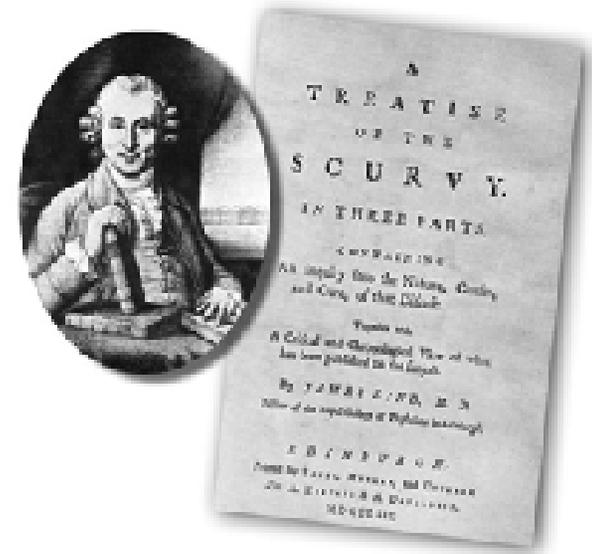
**Advisory Committee to the Director  
December 1, 2006**

**Amy Patterson, M.D.  
Director, Clinical Research Policy  
Analysis and Coordination Program**



# History – First Recorded Clinical Trial

- **Description:** 1747 trial to study interventions for scurvy
- **PI:** James Lind
- **Site:** Onboard the *Salisbury* at sea
- **Study Design**
  - **Participants:** Twelve sailors with scurvy
  - **Six treatment arms (n=2 per arm)**
    - Cider
    - *Elixir vitriol*
    - Vinegar
    - Sea water
    - Concoction of spices, garlic, and mustard seeds
    - Oranges and lemons
- **Publication:** One (*A Treatise of the Scurvy* [1753])



# **Evolving Research Paradigm**

- **The clinical research enterprise is rapidly expanding in scope and complexity.**
- **Clinical research projects are no longer solely local endeavors of large academic medical centers.**
- **As the landscape has grown in complexity, so have the requirements for the conduct and oversight of clinical research.**
  - **Growth by accretion and in a fragmented manner**
  - **Oversight policies often still reflects a time when clinical research was a local enterprise**

# The Need for Harmonization – A Finding of the NIH Roadmap Consultation



# Priority Issues Identified Through Roadmap Consultation

- 1. Adverse event reporting**
- 2. Clinical trial data and safety monitoring**
- 3. Applicability of privacy requirements and HIPAA to clinical research**
- 4. Models of IRB review**
- 5. Best practices in informed consent**
- 6. Variable interpretation of human subjects regulations**
- 7. Science, safety, and ethics in clinical trial design**



# Clinical Research Policy Analysis and Coordination (CRpac) Program

- **Aims**

- **Promote clear, effective, and coordinated policies and regulations for the conduct and oversight of clinical research**
- **Maintain the integrity and enhance the effectiveness of federal and institutional systems of oversight**

- **Methods**

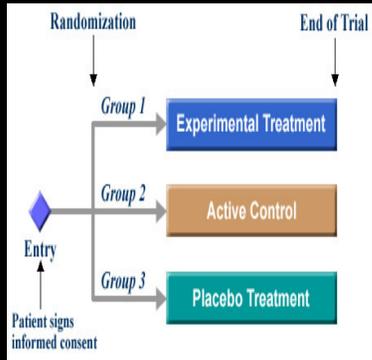
- **Develop tools and resources**
- **Build partnerships and new models of interaction**

# Liaison Activities

- **NIH Liaison to:**
  - **HHS Office of Human Research Protections (OHRP)**
    - **NIH representative to Secretary's Advisory Committee on Human Research Protections (SACHRP)**
  - **Food and Drug Administration (FDA)**
    - **Co-Chair the NIH/FDA Clinical Research Task Force**

# Clinical Research Continuum

## Clinical Trial Design



## IRB Review



## Specimen Collection and Analysis



## Reporting



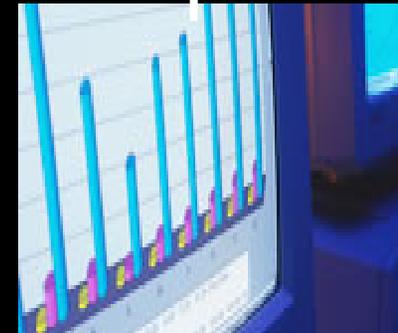
## Protocol Authoring



## Enrollment



## Monitoring



## Analysis

# Current Adverse Event Reporting

The image displays several overlapping forms used for adverse event reporting. The most prominent is the MedWatch form (FDA Form 302A (10/01)), which includes sections for patient information, adverse event or product details, and initial reporter information. Another form, the GEMCRIS Adverse Event Report, is also visible, featuring a structured layout with sections for identification, subject information, reported medical conditions, and event details. The forms are layered, showing different parts of the reporting process.

- Divergent federal reporting policies
- Divergence creates confusion, non-compliance, increased costs
- Poor quality of information
  - No standards
  - Incomplete reports
- Deluge of AERs that cannot be interpreted in multi-site trials
- Potential for negative effect on protection of human subjects



# Federal Adverse Event Task Force

- **Charge**

- Propose specific means for promoting harmonized and streamlined federal requirements for reporting, analyzing, and communicating adverse events in clinical research

- **Member Agencies**

- FDA
- OHRP
- AHRQ
- DoD
- VA
- NIH (chair)
- CDC

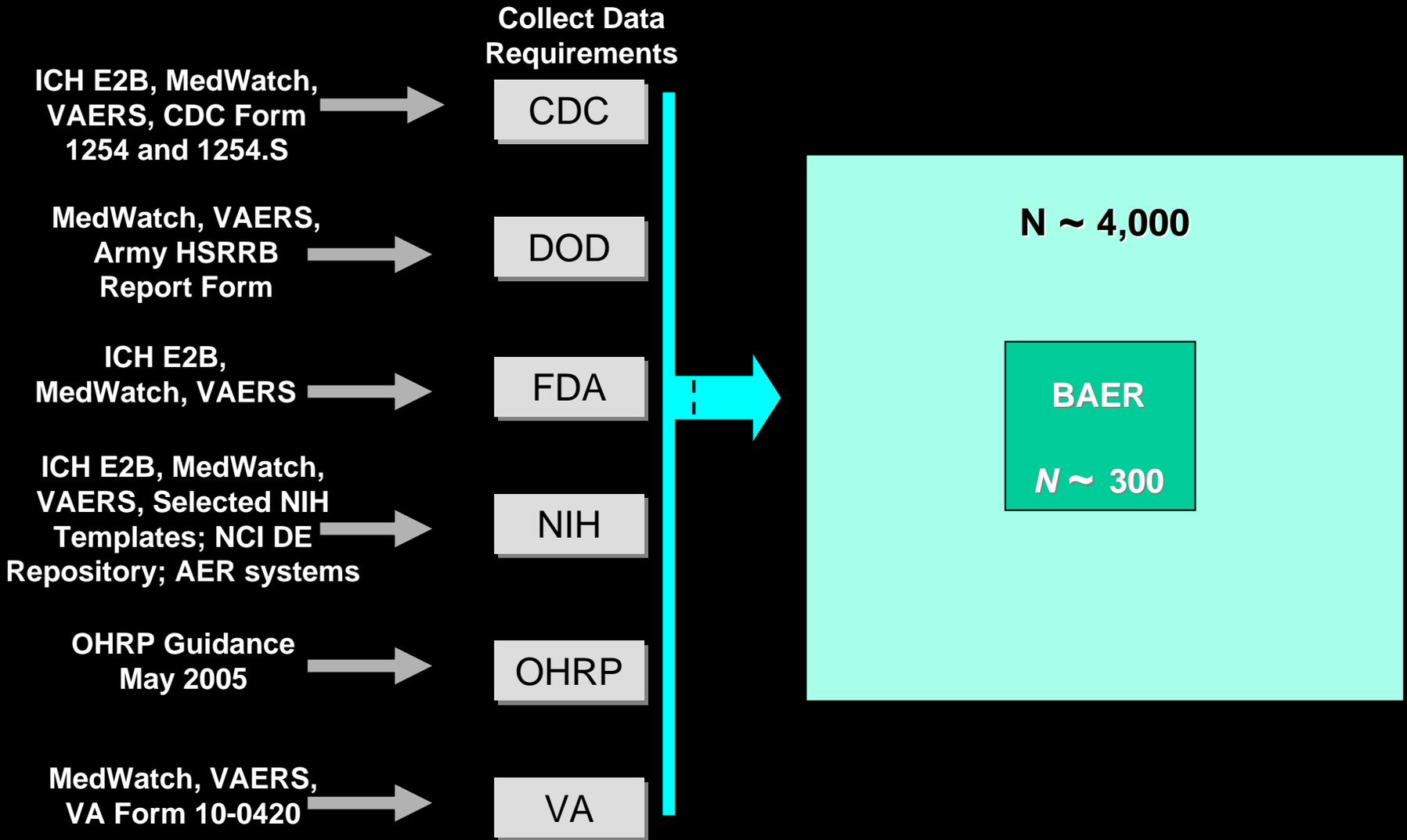
- **Stakeholder Input Strategy**

- Focus groups with individual agencies, IRBs, PIs and industry

# FAET Objectives

1. Agencies will speak the same language
2. Develop *best practices blueprint* for reporting, analysis, and application of safety information
3. One core AE report that PIs can send to multiple agencies
  - Basal Adverse Event Report (BAER)

# How was the BAER developed?



# Key Features of BAER

- **BAER utilizes existing data standards for AE reporting**
  - **International Conference on Harmonization (ICH) E2B**
  - **Health Level 7 (HL7) Individual Case Safety Report (ICSR)**
- **BAER encompasses all forms of clinical research, including interventional studies (e.g., drugs, devices, biologics) and observational studies**

# Key Features of BAER

- **Investigators and practitioners will be able to draw upon a single streamlined data set to report:**
  - **Safety information to:**
    - **Multiple agencies**
    - **IRBs and DSMBs**
  - **Unanticipated problems**
  - **Post-market adverse events to FDA**

# Key Features of BAER

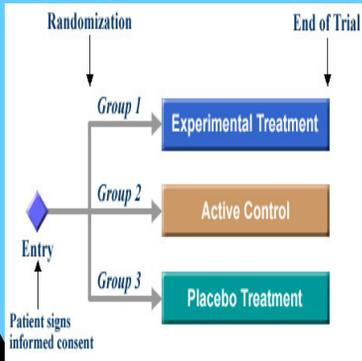
- **Enhances protection of human subjects and patients by enabling a more uniform and streamlined approach to adverse event reporting**
  - **Provides standards and promotes completeness of data**
  - **Improves quality of data**
  - **Facilitates analysis of information**

# Moving Forward

- Briefed the Secretary's Advisory Committee on Human Research Protections (July 31, 2006)
- Further engage IRB and research community
- Web-based application for testing
- Federal Implementation (Phased Approach)
  - Target 2007- 2008

# Clinical Research Continuum

## Clinical Trial Design



## IRB Review



## Specimen Collection and Analysis



## Reporting



## Protocol Authoring



## Enrollment



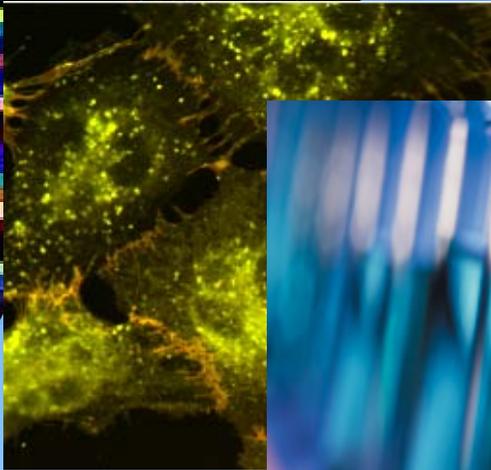
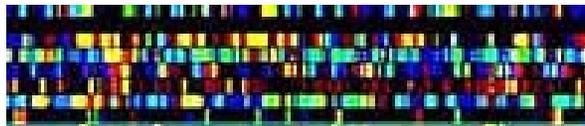
## Monitoring



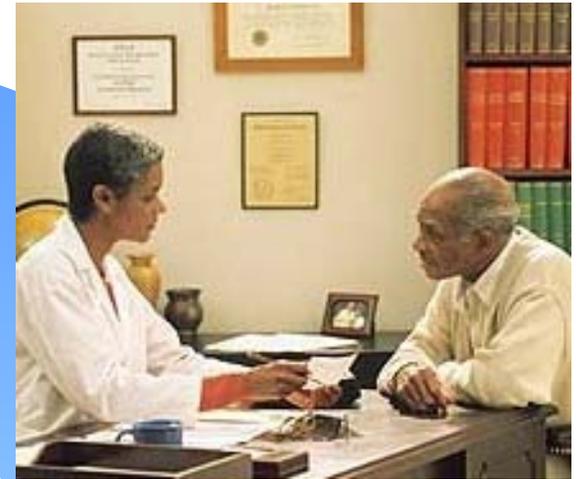
## Analysis

# Science, Safety, and Ethics in Clinical Trial Design

- **Proper trial design is critical to ensuring the scientific validity, safety, and ethics of clinical research**
- **Different design choices have different implications for:**
  - **Applicability of research results to clinical practice (“bedside to practice”)**
  - **Utility of early studies in demonstrating feasibility and safety (“bench to bedside”)**



**Bench**



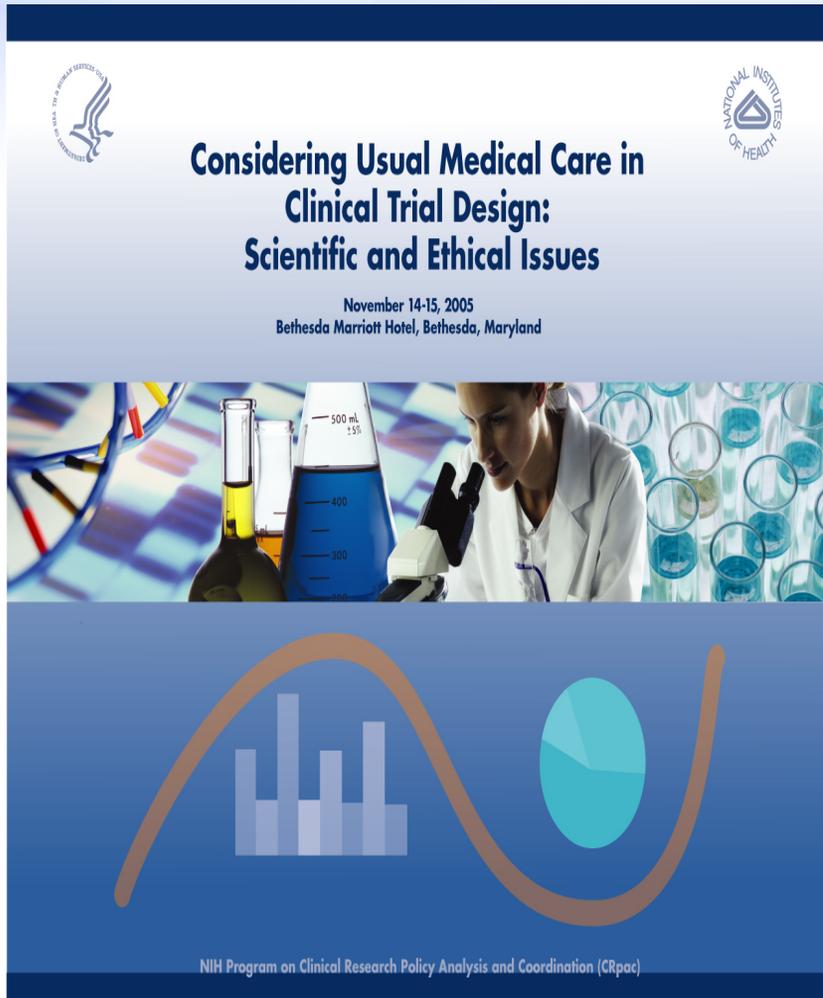
**Medical Practice**

- Standard of Care
- Usual Care



**Research Bedside**

# Usual Care in Clinical Research: *How, When, and Why?*



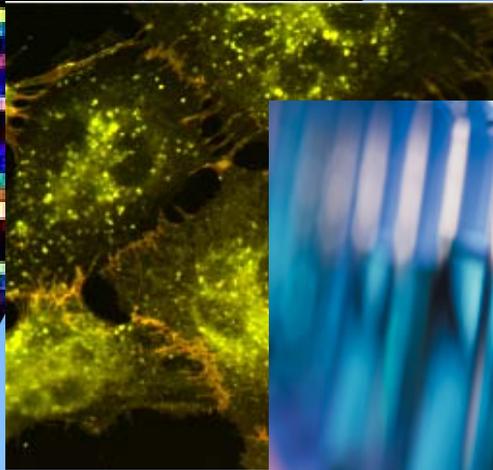
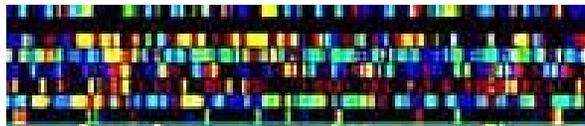
The image shows the cover of a report titled "Considering Usual Medical Care in Clinical Trial Design: Scientific and Ethical Issues". The cover features the logos of the U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH) at the top. The title is prominently displayed in the center, with the dates "November 14-15, 2005" and the location "Bethesda Marriott Hotel, Bethesda, Maryland" below it. The central image depicts a scientist in a white lab coat looking through a microscope, with various laboratory glassware like beakers and flasks in the background. At the bottom, there is a graphic with a blue background, a brown sine wave, a bar chart, and a pie chart. The text at the bottom of the cover reads "NIH Program on Clinical Research Policy Analysis and Coordination (CRpac)".

**Considering Usual Medical Care in  
Clinical Trial Design:  
Scientific and Ethical Issues**

November 14-15, 2005  
Bethesda Marriott Hotel, Bethesda, Maryland

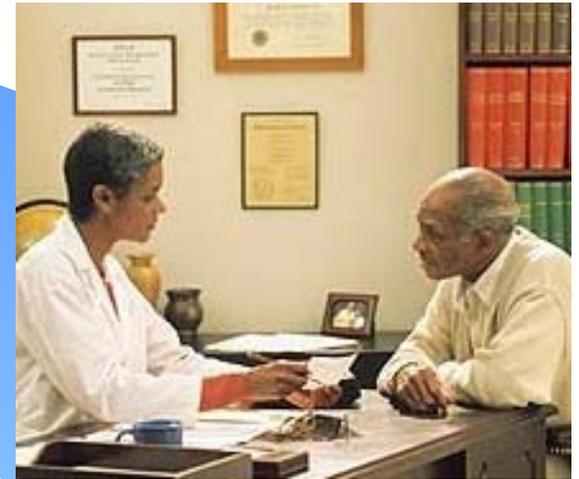
NIH Program on Clinical Research Policy Analysis and Coordination (CRpac)

- **Co-Sponsored by FDA, OHRP, AHRQ, CMS, DoD, DVA and NIH**
- **Outcomes**
  - **Meeting proceedings and video archive**
  - **“Points to Consider” regarding usual care in design and conduct of randomized controlled trials**
- **Requests for follow-up conference**



## Bench

- Phase 0
- Microdosing
- First in humans
- Adaptive trial design



## Medical Practice

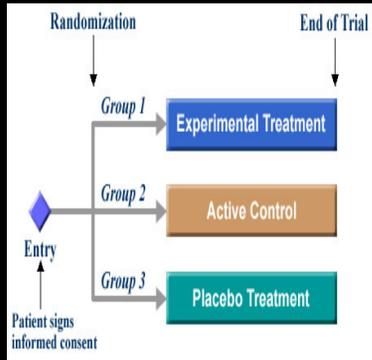
- Standard of Care
- Usual Care



## Research Bedside

# Clinical Research Continuum

## Clinical Trial Design



## IRB Review



## Specimen Collection and Analysis



## Reporting



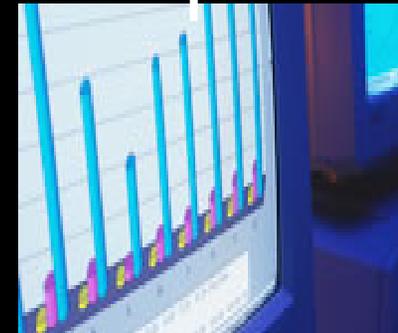
## Protocol Authoring



## Enrollment



## Monitoring



## Analysis

# Optimizing IRB Review: Principles and Potential Models

- **Historically IRBs**
  - Conceptualized at a time when primarily large academic institutions conducted human research
  - Established as a local, institutional body
  - Obligated to consider local context
- **Shifting paradigm**
  - Research increasingly a collaborative enterprise
  - Growing prominence of multi-site trials
  - Central and other alternatives to local IRB review increasingly attractive
    - Efficiency
    - Consistency

# *How can IRB review models be optimized in light of an evolving research landscape?*

- **Alternative IRB Models Emerging**
  - Commercial (e.g., Western, Chesapeake)
  - Reciprocal IRB review (MACRO)
  - Consortia (BRANY)
  - Facilitated review (NCI CIRB)
- **Institutions are resisting alternative IRBs<sup>1</sup> due to:**
  - Liability concerns
  - Desire for local control
  - Misunderstanding of federal policies

<sup>1</sup>*Academic Medicine*, July 2004

# Optimizing IRB Review: Need for National Dialogue

- **National Conference –**
  - **November 20-21, 2006**
- **Sponsors**
  - **NIH CRpac, OHRP, VA, DoD, AAMC, ASCO, PRIM&R, AAU, COGR, COSSA, NACUA**
- **Explored:**
  - **Shared responsibility between institutions and independent review boards**
  - **Characteristics of alternative IRBs and impact on quality of review**
  - **Liability issues**
  - **Economic considerations**

**Save the Date**  
**November 20-21, 2006**

Program runs 8:30 a.m.–5 p.m. on Monday, November 20, and 8:30 a.m.–12:30 p.m. on Tuesday, November 21. Registration will open at 5 p.m. on Sunday, November 19.

**National Conference on Alternative IRB Models: Optimizing Human Subject Protection**

Wardman Park Marriott  
Washington, DC

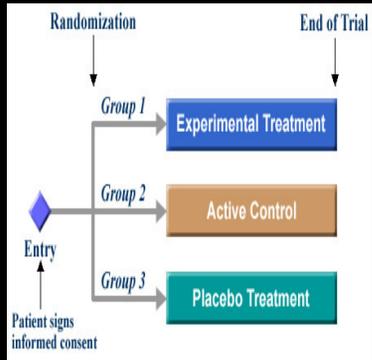
    

Co-Sponsored by: AAU, COGR, COSSA, DOD, NACUA, and PRIM&R

Everyone is welcome to attend, but the conference is designed especially for individuals who are involved in decisions about whether their institutions should use an alternative to local IRBs, for example, institutional officials, institutional legal counsel, investigators, sponsors, subjects and their advocates, representatives of trial management organizations, research deans, IRB chairs and members, IRB administrators, and government regulators.

# Clinical Research Continuum

**Clinical Trial Design**



**IRB Review**



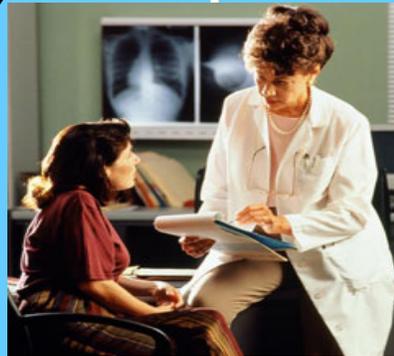
**Specimen Collection and Analysis**



**Reporting**



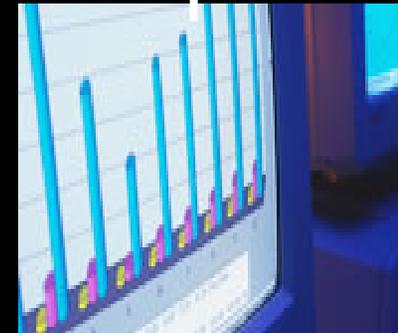
**Protocol Authoring**



**Enrollment**

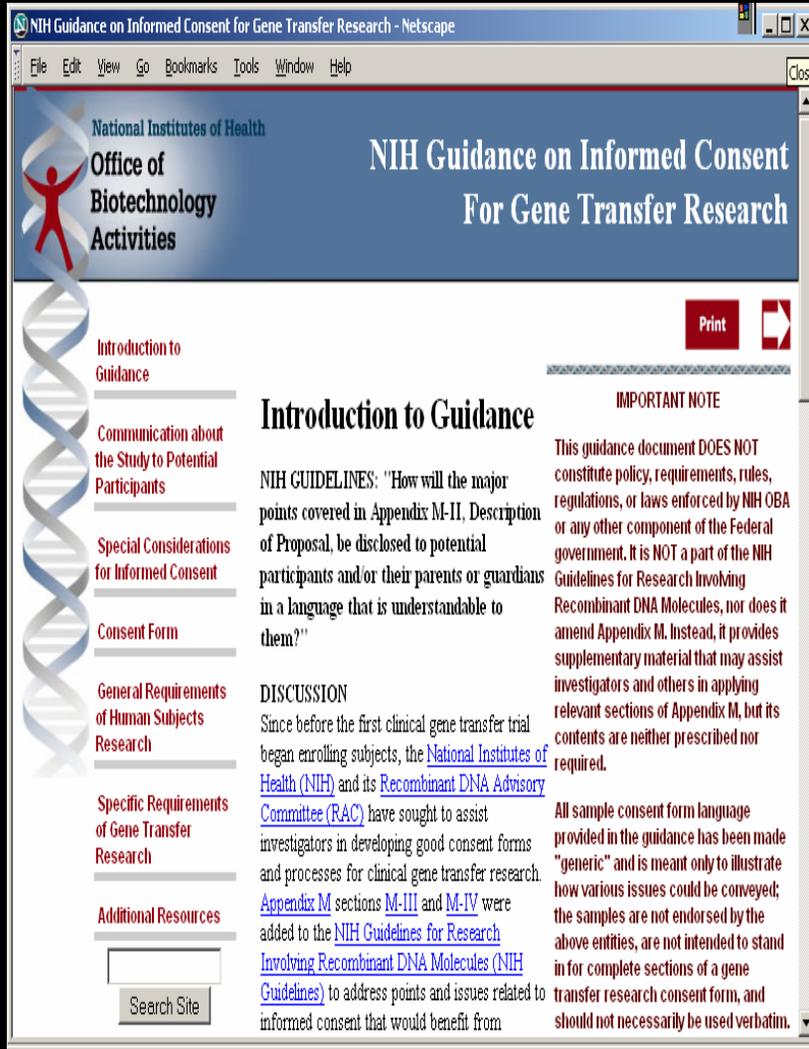


**Monitoring**



**Analysis**

# Informed Consent



The screenshot shows a Netscape browser window displaying the NIH website. The page title is "NIH Guidance on Informed Consent for Gene Transfer Research - Netscape". The browser's menu bar includes "File", "Edit", "View", "Go", "Bookmarks", "Tools", "Window", and "Help". The website header features the NIH logo and the text "National Institutes of Health Office of Biotechnology Activities" and "NIH Guidance on Informed Consent For Gene Transfer Research". A navigation menu on the left lists: "Introduction to Guidance", "Communication about the Study to Potential Participants", "Special Considerations for Informed Consent", "Consent Form", "General Requirements of Human Subjects Research", "Specific Requirements of Gene Transfer Research", and "Additional Resources". The main content area is titled "Introduction to Guidance" and includes an "IMPORTANT NOTE" section. A search box is located at the bottom left of the page.

NIH Guidance on Informed Consent  
For Gene Transfer Research

Introduction to Guidance

Communication about the Study to Potential Participants

Special Considerations for Informed Consent

Consent Form

General Requirements of Human Subjects Research

Specific Requirements of Gene Transfer Research

Additional Resources

Search Site

**Introduction to Guidance**

NIH GUIDELINES: "How will the major points covered in Appendix M-II, Description of Proposal, be disclosed to potential participants and/or their parents or guardians in a language that is understandable to them?"

**DISCUSSION**

Since before the first clinical gene transfer trial began enrolling subjects, the [National Institutes of Health \(NIH\)](#) and its [Recombinant DNA Advisory Committee \(RAC\)](#) have sought to assist investigators in developing good consent forms and processes for clinical gene transfer research. [Appendix M](#) sections [M-III](#) and [M-IV](#) were added to the [NIH Guidelines for Research Involving Recombinant DNA Molecules \(NIH Guidelines\)](#) to address points and issues related to informed consent that would benefit from

**IMPORTANT NOTE**

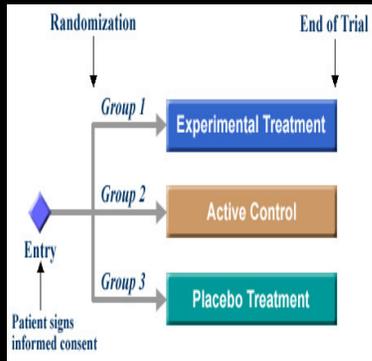
This guidance document DOES NOT constitute policy, requirements, rules, regulations, or laws enforced by NIH OBA or any other component of the Federal government. It is NOT a part of the NIH Guidelines for Research Involving Recombinant DNA Molecules, nor does it amend Appendix M. Instead, it provides supplementary material that may assist investigators and others in applying relevant sections of Appendix M, but its contents are neither prescribed nor required.

All sample consent form language provided in the guidance has been made "generic" and is meant only to illustrate how various issues could be conveyed; the samples are not endorsed by the above entities, are not intended to stand in for complete sections of a gene transfer research consent form, and should not necessarily be used verbatim.

- Processes and expectations have become increasingly more complex
  - Esp. for certain areas of research (hi-tech, hi-risk)
- Need for tools and resources to optimize the effectiveness and value of the informed consent process
- Pilot project developed with OHRP, FDA, RAC
  - Informed consent for gene transfer research
  - <http://www4.od.nih.gov/oba/rac/ic/>

# Clinical Research Continuum

## Clinical Trial Design



## IRB Review



## Specimen Collection and Analysis



## Reporting



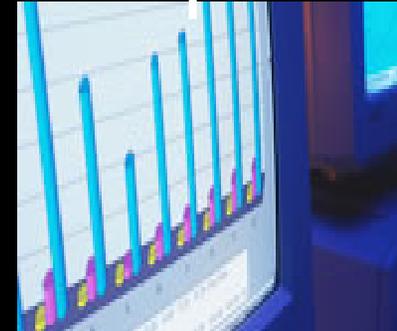
## Protocol Authoring



## Enrollment



## Monitoring



## Analysis

# Research Using Specimens and Data Repositories



- **Disharmony in regulations and policies**
  - Creates barriers to biobanking and sharing data
- **Guidance needed to clarify complex issues**
  - e.g., ownership, intellectual property, return of research results

- **Two tiered approach:**

- **Trans-NIH Task Force**
  - Common framework for addressing ELSI issues
- **Trans-HHS Task Force**
  - OHRP, FDA, AHRQ, CDC, NIH
  - Work toward more consistent policies

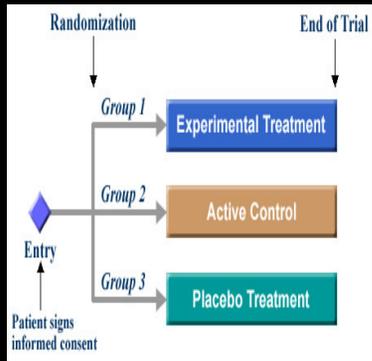
# Privacy And Confidentiality



- **Is the HIPAA Privacy Rule adversely affecting clinical research?**
  - ***Examples:***
    - **National clinical research networks**
    - **Phenotypic datasets**
- **Need for more systematic information regarding the impact of the Rule**
  - **Institute of Medicine study planned**

# Clinical Research Continuum

## Clinical Trial Design



## IRB Review



## Specimen Collection and Analysis



## Reporting



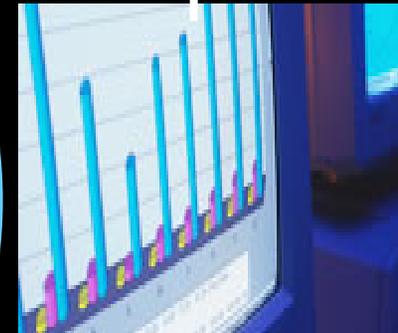
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## Analysis

# Data Safety and Monitoring Boards

- **Current Policy**

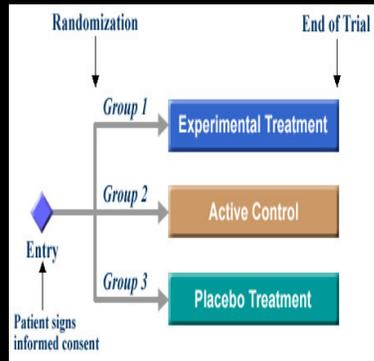
- All NIH clinical trials must have a data monitoring plan; *certain* types require a DSMB

- **Need to Clarify**

- When DSMBs are necessary
- Roles and responsibilities of DSMBs with regard to other clinical trial monitoring mechanisms
- Best Practices and Standard Operating Policy and Procedures
  - Best practices in data review
  - Independence of DSMB members from trial, institution, agency/sponsor
  - Roles and responsibilities – operational or advisory?
  - Lines of communication
  - COI screening

# Clinical Research Continuum

## Clinical Trial Design



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## Reporting



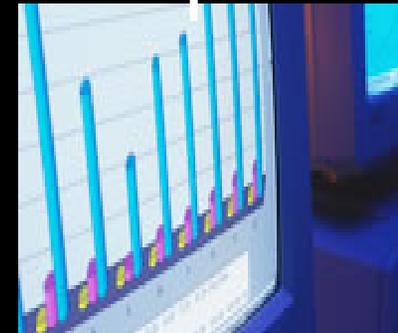
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## Analysis





# Clinical Research

## Policy Analysis & Coordination

[Home](#)[Program Overview](#)[Issues and Activities](#)[Conferences and Meetings](#)[Key Policies & Regulations](#)[Tools and Resources](#)[Contact Us](#)

### Program Overview

Clinical research is one of the nation's most vital undertakings, leading to improved medical care, new diagnostic, preventative, and therapeutic methods, and improved quality of life for patients and their families. It is widely recognized, however, that the efficiency and effectiveness of our system of clinical research is hampered by variability in regulations and policies that pertain to the conduct and oversight of clinical research. This has created in turn a measure of burden on the research community to understand and fulfill multiple requirements that may be duplicative or even conflicting. This variability exists among various federal agencies that support and oversee clinical research, as well as among the Institutes and Centers of the NIH itself.

The NIH has created a Clinical Research Policy Analysis and Coordination (CRpac) Program to serve as a focal point for the ongoing harmonization, streamlining, and optimization of policies and requirements concerning the conduct and oversight of clinical research. The CRpac program reflects the responsibility of the NIH, as the lead federal agency supporting clinical research, to promote the efficiency and effectiveness of the clinical research enterprise, in part by facilitating compliance and oversight.

The CRpac Program, housed within the Office of Science Policy in the Office of the NIH Director, works on an array of issues and activities on behalf of all NIH components. The program's objective is to develop and implement coordinated policies and practices reflective of the needs and points of view of NIH's varied organizational components and stakeholders. CRpac staff work closely with other Federal agencies and offices that have responsibilities concerning the oversight of clinical research, including the Office of Human Research Protections, the Food and Drug Administration, the Department of the Veterans Administration, the Department of Defense, and other Federal agencies that have adopted the Common Rule.

Some specific foci for this effort include:

- Harmonizing diverse adverse event reporting requirements;
- Clarifying the respective roles and responsibilities of Data Safety and Monitoring Boards (DSMBs) and other review mechanisms;
- Clarifying policy where variability in the application of the human subjects regulations exists;
- Examining the characteristics and features of various models of IRB review and considering their advantages for forms of research activities;
- Studying various approaches to providing informed consent and sharing best practices; and
- Creating dialogue on promoting science, safety, and ethics through clinical trial design.

# CRpac Contact

Clinical Research Policy Analysis and  
Coordination Program

Office of the Director

Office of Science Policy

National Institutes of Health

Website: <http://crpac.od.nih.gov>

